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Margaret H. Collins, MD, Series Editor, and Giulio J. D'Angio, MD, Co-Editor*

Hodgkin Disease?

Audrey E. Evans, MD,[1] Margaret H. Collins, MD,[2] Eli Glatstein, MD,[3] and G. Peter Feola, MD[4]

Audrey E. Evans, MD (Pediatric Oncologist)

The patient under discussion today presents some difficult decisions regarding both diagnosis and management.

History of present illness. The patient is a healthy, active 13-year-old male who, since the age of 3 or 4 years, has had a small lump in his left groin ''about ¾ of an inch'' in diameter; i.e., 2 cm according to the parents. It changes in size, has never been painful, and was thought by his pediatrician to be a reactive lymph node. Seven months ago, while playing football, he was hit in the groin and the node became painful. His mother thought it seemed to be larger, but the patient does not agree. His physician felt it should be biopsied and the final histologic report was lymphocyte predominant nodular Hodgkin disease (LPHD). This diagnosis was confirmed in this institution and by a consultant who is an acknowledged expert in the pathology of lymphomatous processes.

The patient's general health is excellent: he is very active, plays sports, has experienced no weight loss, night sweats, or chills, and has no family illnesses. Except as noted, his past history is non-contributory and his development was normal.

Physical examination. On admission, the patient was a healthy-looking, chunky white male: temperature 37.1°C, height 155 cm, weight 66.8 kg, m^2 1.65, blood pressure 114/60, heart rate 77, respirations 20. The only abnormal physical findings were a well-healed surgical incision in the left groin and a 1 cm node in the right groin. There was no other lymphadenopathy.

Laboratory findings. Hemoglobin 14.6, platelets 199,000, white count 6.4, granulocytes 47%, lymphocytes 45%, atypical monocytes 2, eosinophils 2, sedimentation rate 0, ferritin 22.3, lactate dehydrogenase 490. Skin tests for tetanus, candida, and mumps were positive; chest X-ray film was negative; gallium scan was negative. Computed tomographic (CT) scan findings will be discussed, but the report indicated right iliac and left inguinal adenopathy consistent with the diagnosis of Hodgkin disease (HD).

His treatment has consisted of four courses of cyclophosphamide, vincristine, and procarbazine on week 1, and doxorubicin, bleomycin, and vinblastine on week 2, repeated on day 28. He has tolerated treatment well, and the CT scan at the end of treatment shows reduction in the size of the right iliac and left inguinal nodes.

The questions to be discussed are: 1) Does this patient have HD? 2) If so, is he in complete remission? 3) Is he a suitable candidate for an HD randomized clinical trial?

Michael Needle, MD (Pediatric Oncologist)

Let me understand: This lump has been present for 10 years?

Dr. Evans So it would seem. Both the pediatrician and the family attest to that.

Giulio J. D'Angio, MD (Pediatric Radiation Oncologist)

Dr. Evans, can you explain why skin tests were performed?

Dr. Evans Skin tests were often used in past years to document the anergy exhibited by HD patients [1]. This boy reacted to all of the tests. While the diagnosis is not excluded by this result and the clinical findings, they do

[1]Division of Oncology, Children's Hospital of Philadelphia, Philadelphia, Pennsylvania.

[2]Department of Pathology, Children's Hospital of Philadelphia, Philadelphia, Pennsylvania.

[3]Department of Radiation Oncology, Hospital of the University of Pennsylvania, Philadelphia, Pennsylvania.

[4]Department of Radiology, Hospital of the University of Pennsylvania, Philadelphia, Pennsylvania.

*Correspondence to: Giulio J. D'Angio, Radiation Oncology/2 Donner, Hospital of the University of Pennsylvania, 3400 Spruce Street, Philadelphia, PA 19104.

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not support the histologic diagnosis, either. Dr. Feola, could you now show us the imaging studies?

G. Peter Feola, MD (Radiology Fellow)

My understanding is that these studies were obtained after excisional biopsy of the left groin node. There remains, however, a 2 × 3 cm node visible in the left groin. In addition, there is a 2.5 × 1 cm node seen high in the right iliac chain just at the aortic bifurcation. There is no other evidence of lymphadenopathy on either side (Fig. 1). A gallium scan was performed and was negative.

The scans obtained after chemotherapy show the same two nodes which are much reduced in size but are still present (Fig. 2).

Dr. Evans Dr. Collins, could you please now discuss the histopathology obtained at the time of diagnosis?

Margaret H. Collins, MD (Pediatric Pathologist)

There was much discussion concerning the histopathology of the excised lymph node. The node is effaced by a nodular infiltrate of lymphocytes and histiocytes. Classic Reed-Sternberg cells are absent but variants of Reed-Sternberg cells are present. These variants are cells with lobated or folded nuclei and inconspicuous nucleoli (Fig. 3) and are so-called ''popcorn'' cells. These cells are characteristic of lymphocyte predominant (lymphocytic and histiocytic) Hodgkin disease (LPHD) of Lukes and Butler [2]. Inflammatory cells, such as eosinophils and plasma cells, are present in very small numbers in this case as in all cases of nodular LPHD

LPHD differs from the other types of HD in several ways. Paucity or absence of classic Reed-Sternberg cells, presence of polypoid or ''popcorn'' variants of Reed-Sternberg cells, and predominance of lymphocytes and reactive histiocytes are the characteristic histologic features that distinguish LPHD from the other types of HD. The immunophenotype of LPHD also differs. Classic Reed-Sternberg cells stain with CD15 (Leu-M1) and CD30 (Ki-1) but not with CD45 (leukocyte common antigen) antibodies; Reed-Sternberg variants in LPHD stain with CD45 but generally not with CD15 or CD30 antibodies. The immunophenotype of this case is consistent with LPHD. Immunoglobulin light chain restriction characterizes LPHD but not the other types of HD [3,4]. The many histologic and clinical differences between LPHD and the other forms of the disease have led to the proposal that LPHD should be separated from ''classic'' HD [5].

Garrett M. Brodeur, MD (Pediatric Oncologist)

Did the patient have elevated titers for Epstein-Barr virus (EBV)?

Dr. Collins No, but actually only a small fraction of patients with LPHD are positive. Those with nodular sclerosis usually are, of course [6].

Dr. Evans We have been confronted with a therapeutic dilemma and diagnostic puzzle. Does this patient have HD? If so, is he in complete remission? Finally, is he a suitable candidate for any study concerning HD; e.g., would he be a suitable candidate for a randomized clinical trial, especially one in which the question is whether irradiation of the original site(s) confers a benefit?

We have invited Dr. Eli Glatstein, an internationally recognized expert on HD, to help us sort through these issues.

Eli Glatstein, MD (Radiation Oncologist)

Let me immediately address your first question, and say that I am not convinced that this boy has HD. One thing against it is, of course, the long latent period of 10 years when the node had not changed appreciably in size. First, non-Hodgkin lymphoma can have an extremely long latent period before it manifests itself as a frank neoplastic process. HD can do so, too, but 10 years seems excessive. Also, lymphoproliferative responses to various stimuli can produce lymph nodes like this; indeed, some may evolve with Reed-Sternberg cells. I also am not convinced that the moderately enlarged lymph node seen high in the right iliac chain is part of the same process, and would not accept it as a manifestation of HD. The distribution would be extremely bizarre; i.e., to find an isolated node on the opposite side and one echelon removed is most unusual. This is one instance, incidentally, where lymphangiography might have been of help. It is a procedure that has fallen out of favor for various reasons. Nonetheless, the characteristic foamy reticular appearance of the contrast compound, when present, helps in reaching a diagnosis. In dealing with diagnostic issues of lymphoma, we seek to distinguish reliably between lymphoproliferation secondary to neoplasia and lymphoproliferation due to inflammation.

To deal with your second question, i.e., whether he is in complete remission, it is moot since I am not confident that he has HD in the first place. To answer your third question, no, I do not believe he is a suitable candidate for any study dealing with HD for the same reason.

Dr. Brodeur Studies at the molecular level could help in a patient like this; e.g., to try to establish clonality. Most of the cells from a lymph node in a patient with HD are not malignant, of course, but Feulgen-stained preparations are helpful in reaching conclusions concerning the chromosomal content. Also, studies of ploidy may assist in reaching a conclusion regarding the presence of malignant cells. The same can be said for a histogram of cell ploidy.

Dr. Glatstein Cells in lymph node specimens in patients with mononucleosis can show evidence of Reed-Sternberg cells, and that is a non-neoplastic condition [7]. Similarly, inflammatory processes can sometimes be

Fig. 1. Contrast enhanced helical CT (8 mm slice thickness) demonstrates **(a)** a 2 × 3 cm enlarged lymph node with an adjacent node in the left groin (straight arrow) anterior to the common femoral artery and vein (curved arrow) and **(b)** a 2.5 × 1 cm enlarged lymph node in the right iliac chain (straight arrow) adjacent to the bifurcation of the aorta and inferior vena cava (curved arrow).

Fig. 2. Contrast enhanced helical CT (8 mm slice thickness) after chemotherapy shows **(a)** marked reduction in the size of the enlarged lymph nodes in the left groin (straight arrow) anterior to the common femoral artery and vein (curved arrow) as well as **(b)** in the right iliac chain (straight arrow). Curved arrow indicates the bifurcation of the aorta and inferior vena cava.

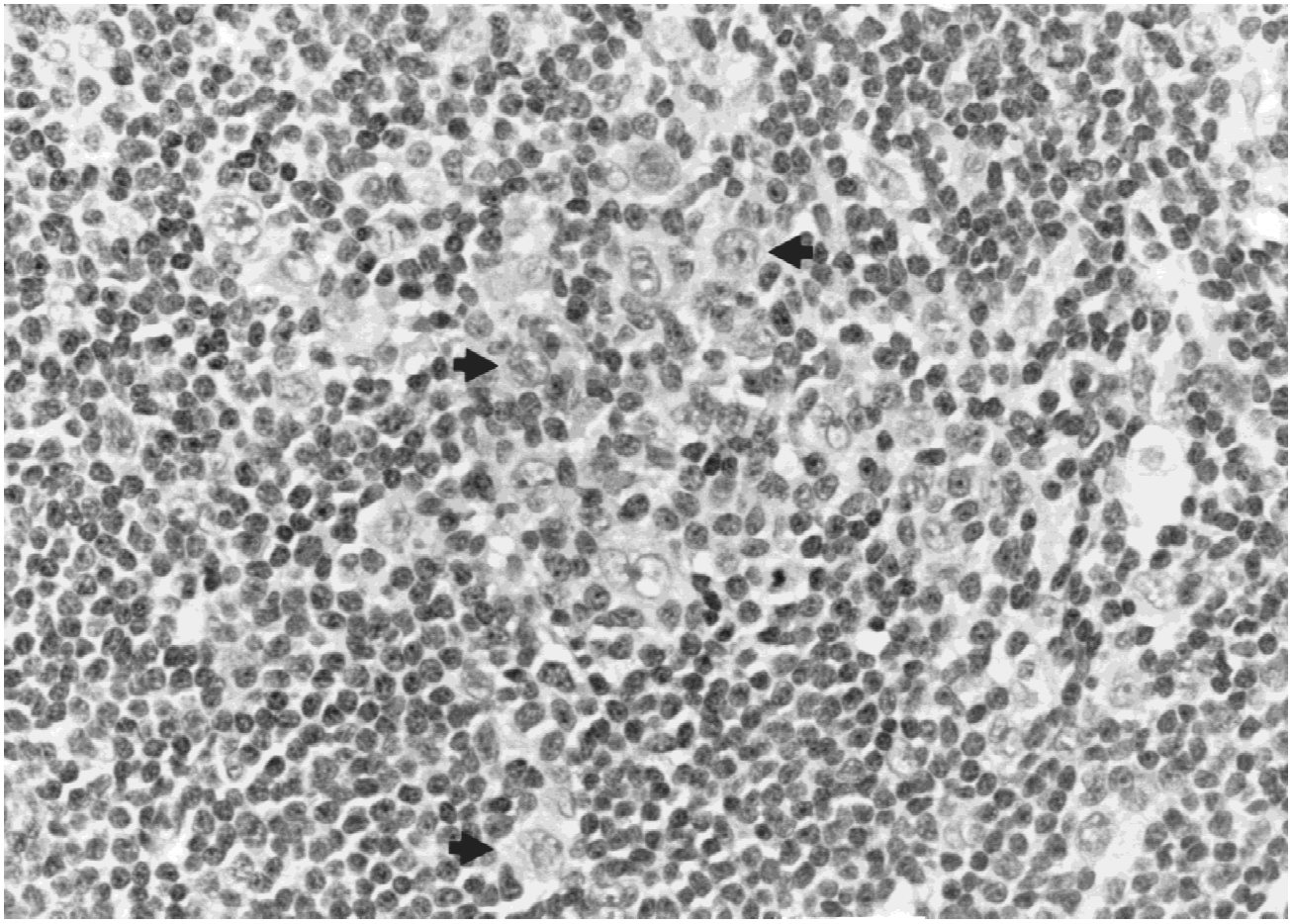

Fig. 3. This field contains several so-called ''popcorn'' cells (arrows).

monoclonal [8]. On the other hand, aneuploidy is a characteristic of HD [9].

Dr. Evans When all is said and done, Dr. Glatstein, what course would you recommend?

Dr. Glatstein I would do nothing more at this time. Indeed, this is the kind of patient I have elected not to treat at the time of initial diagnosis in favor of a policy of careful follow-up. When and if the disease declared itself, there was time to move forward with effective therapy. I believe such a course is reasonable given the very uncertain nature of this boy's problem. I understand there is a study where he could be randomized at this point to either receive or not receive radiation therapy; personally, I would not include such an unusual case.

Joel Goldwein, MD (Pediatric Radiation Oncologist)

Where would you irradiate?

Dr. Glatstein Precisely the question; I do not know. Therefore, my advice would be to have frequent follow-up visits with careful physical examinations, imaging studies only when indicated, and re-biopsy if and when the left inguinal node (or any other) enlarges. There should be time to devise a perfectly sound and effective treatment strategy should a subsequent biopsy reveal an unequivocal diagnosis.

Dr. Evans The excellent paper by Karayalcin et al. [10] reports 26 patients with LPHD out of 613 patients with HD entered on 5 clinical studies by members of the Pediatric Oncology Group (POG). Twenty-two of the 26 were boys with a mean age of 12.9 years, 10 had multiple sites of involvement including bilateral disease in 3, one of whom had an axilla and the contralateral inguinal region involved. All patients did well on various forms of treatment and the only two deaths arose from second malignant neoplasms (SMN), presumably linked to the treatments given. The authors conclude that, ''The optimal treatment for LPHD should focus on efforts to limit the risk of SMNs'' and are suggesting surgery alone might suffice for some such children. This is almost a heretical suggestion, but it was not long ago that children with early stage neuroblastoma (1 and 2A) were given full combined modality therapy. We now know that such aggressive treatment is not necessary [11]. Indeed, the issue is being raised in a subset of Wilms tumor infants in the National Wilms Tumor Study (NWTS-5) [12].

Returning to our patient, the question is not so much

whether he has LPHD; he fits the description in the POG study [10]. The questions are: What is LPHD? How malignant is the process that bears that designation? Close observation fits well with Dr. Glatstein's reluctance to add radiation therapy. Also, one has to wonder about the need for any treatment when so-called cancers of the types just discussed can be cured by minimal means. Perhaps for the patient under discussion, close observation might have been the best management from the beginning, as would have been Dr. Glatstein's policy. We will continue to follow him without further treatment.

ADDENDUM

The patient has been followed 12 months since diagnosis and remains well. A CT scan 6 months after completion of treatment showed no residual lymphadenopathy. Since this Tumor Board, clonality of ''popcorn'' cells has been reported [13,14]. The immunoglobulin variable-region gene mutations of Reed-Sternberg cells differ from those of cells in LPHD, another feature that distinguishes LPHD from ''classic'' HD [15].

REFERENCES

1. Slivnick DJ, Ellis TM, Nawrocki JF, Fisher RI: The impact of Hodgkin's disease on the immune system. Semin Oncol 17:673–682, 1990.
2. Lukes RJ, Butler JJ: The pathology and nomenclature of Hodgkin's disease. Cancer Res 26:1063–1081, 1966.
3. Stoler MH, Nichols GE, Symbula M, Weiss LM: Lymphocyte predominance Hodgkin's disease. Evidence for a k light chain-restricted monotypic B-cell neoplasm. Am J Pathol 146:810–818, 1995.
4. Von Waseilewski R, Werner M, Fischer R, et al. Lymphocyte-predominant Hodgkin's disease. An immunohistochemical analysis of 208 reviewed Hodgkin's disease cases from the German Hodgkin Study Group. Am J Pathol 150:793–803, 1997.
5. Mason DY, Banks PM, Chan J, et al. Nodular lymphocyte predominance Hodgkin's disease. A distinct clinicopathological entity (editorial). Am J Surg Pathol 18:526–530, 1994.
6. Andriko JW, Aguilera NS, Nandedkar MA, Abbondanzo SL: Childhood Hodgkin's disease in the United States: An analysis of histologic subtypes and association with Epstein-Barr virus. Mod Pathol 10:366–371, 1997.
7. Lukes RJ, Tindle BH, Parker JW: Reed-Sternberg-like cells in infectious mononucleosis. Lancet 22:1003–1004, 1969.
8. Limpens J, deJong D, Van Kriekan JHJM, Price CGA, et al.: Bel-2/Jh rearrangement in benign lymphoid tissues with follicular hyperplasia. Oncogene 6:2271–2276, 1991.
9. Seef GSF, Spriggs AS: Chromosome changes in Hodgkin's disease. J Natl Cancer Inst 39:557–570, 1967.
10. Karayalcin G, Behm FG, Gieser PW, et al.: Lymphocyte predominant Hodgkin's disease: Clinico-pathologic features and results of treatment: The Pediatric Oncology Group experience. Med Pediatr Oncol 29:519–525, 1997.
11. Evans AE, Silber JH, Shpilsky A, D'Angio GJ: Successful management of low-stage neuroblastoma with adjuvant therapies: A comparison of two decades, 1972 through 1981 and 1982 through 1992, in a single institution. J Clin Oncol 14:2405–2410, 1996.
12. Green DM, Breslow NE, Beckwith JB, et al.: Treatment outcomes in patients less than 2 years of age with small, stage I favorable-histology Wilms' tumors: A report from the National Wilms' Tumor Study. J Clin Oncol 11:91–95, 1993.
13. Marafioti T, Hummel M, Anagnostopoulos I, et al.: Origin of nodular lymphocyte-predominant Hodgkin's disease from a clonal expansion of highly mutated germinal-center B cells. N Engl J Med 337:453–458, 1997.
14. Ohno T, Stribley JA, Wu G, et al.: Clonality in nodular lymphocyte-predominant Hodgkin's disease. N Engl L Med 337:459–465, 1997.
15. Schwartz RS: Hodgkin's disease–Time for a change. N Engl J Med 337:495–496, 1997.

CO-EDITOR'S NOTE

The life and career of Dr. Thomas Hodgkin (1798–1866) have already been reviewed in these pages by Zantinga, and Coppes [Med Pediatr Oncol 27:122, 1996]. It will be recalled that Dr. Hodgkin's inquisitive mind led him to Paris to learn the new technique of stethoscopic auscultation originated by Laënnec and to bring this advance in physical diagnosis back to Guy's Hospital in London.

Reneé Théophile Hyacinthe Laénnec (1781–1826) was a leading French physician who became a professor at the Collège de France and senior physician at the Hôpital de la Charité in Paris. He invented the stethoscope, and is therefore considered one of the fathers of modern physical diagnosis along with such others as the Hungarian Baron Alexander von Korányi (1828–1913), who devised the still commonly practiced method for percussing the chest.

Sir Thomas Guy (1644–1724) built his fortune through the printing and sale of bibles and by shrewd investments. A bachelor, he lived simply—in fact, the term ''skinflint''[1] was applied to him. He nonetheless was a champion of the underprivileged and his generous philanthropy belies his being called a miser. His initial contributions were to St. Thomas's Hospital in London, but the wing he added became the separate institution, Guy's Hospital, in 1722.

Popcorn (of the ''popcorn'' cell) is one of the thousands of varieties of maize (from the West Indian *mahís*).[2] Popcorn was known to the Indians from pre-Colombian times. Corn, an inclusive term, is often applied to the leading cereal grown in a particular region.

[1]Flint is a hard stone which, when struck against steel, creates a spark and is used even today to start fires. It is easily flaked, and small amounts for ready use can be broken from a larger piece. The derogatory term ''skinflint'' thus conjured up one so miserly that he would ''skin a flint'' to get the final, smallest bits before spending a few pennies to buy a new one.

[2]Source for some of the discussion regarding corn: Visser M (ed): ''Much Depends on Dinner.'' New York: Macmillan, 1986.

Thus, ''corn'' in England usually signifies wheat,[3] while in Scotland and Ireland, oats[3] or barley[3] is meant. ''Corn'' in North American is equated with maize or what is called ''Indian corn'' in many parts of the world. Interestingly, it is ''granoturco'' (Turkish grain) in Italian, probably for the same reason that turkeys are given their name. The cheapest and most efficient foods were used by the Turks to feed their dominions. These food items became identified with Turkey even though they originated elsewhere—in these two cases, from the New World. It is of passing interest that one of the specialty (and delicious) dishes identified with the Veneto region of Italy and, specifically, Vicenza (the city of the great architect Andrea Palladio), is polenta[4] (corn meal mush) and baccalà[4] (salt cod), both also being of New World origin.

Corn is the leading grain crop in the United States, which grows more corn than all the rest of the world together. Three-quarters of the amount raised is used to feed cattle (in the generic sense of that word, which includes all domesticated quadrupeds, i.e., four-footed animals).

It is an extraordinarily useful plant. Aside from its benefits as a foodstuff, derivative products in one form or another are to be found in every manufactured product in common use. Resins, adhesives, waxes, oils, lubricants, construction materials, paints, fuels, and a myriad (Greek: 10,000; countless) of other products are derived from maize. The annual yield is usually worth more than all of the other vegetable products raised in the United States, and more than all of the steel, iron, gold, and silver produced.

Some turkey!

[3]All of these are of North European origin, wheat being from the Gothic *hwaites*—white.

[4]Polenta (from Latin *pollen* = fine flour) is made from the hulled, crushed grains of barley, wheat, or other plants, but is now identified with maize; baccalà is derived deviously from North European roots for ''head,'' recalling the large head of the fish.